Short term mortality outcomes of HIV-associated Cryptococcal meningitis in antiretroviral therapy naïve and experienced patients in sub-Saharan Africa

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Abstract

Background

Many patients with cryptococcal meningitis have had antiretroviral therapy (ART) prior to presentation. A recent study found increased short-term mortality in those receiving ART for less than 14 days compared with those on ART for more than 2 weeks. However, presentation and outcomes for patients who have recently initiated ART, and those with virologic failure and/or non-adherence are not well described.

Methods

678 adults with first episode of cryptococcal meningitis recruited into a randomized, non-inferiority, multicentre phase 3 trial in 4 sub-Saharan countries were analysed to compare clinical presentation and 2-and 10-week mortality outcomes between ART-naive and experienced patients, and between patients receiving ART for varying durations prior to presentation.

Results

Over half (56% (381/678)) the patients diagnosed with a first episode of cryptococcal meningitis were ART-experienced. All-cause mortality was similar at 2-weeks (17% vs 20%, p=0.39; HR 0.85, 95%CI 0.6-1.2, p=0.35), and 10 weeks (38% vs 36%, p=0.64; HR 1.03, 95%CI 0.8-1.32, p=0.82) for ART-experienced vs ART-naïve patients, respectively. Among ART-experienced patients, exploring varying cut-off points for ART duration, there were no significant differences in 2- and 10-week mortality based on duration of ART. Using a 2-week cut off, there was a trend towards higher 2-week mortality for those taking ART for ≤ 2 weeks (23% vs 15% 2-week mortality, p=0.15; HR 1.70, 95% CI 0.85 to 3.39, p=0.13).

Conclusion

There were no significant differences in mortality at 2-and 10-weeks between ART- naive and experienced patients, and between ART-experienced patients according to duration on ART. More studies are needed to describe characteristics and outcomes of ART-experienced patients according to duration on ART.

Key words

HIV, Cryptococcal meningitis, Short-term mortality, Antiretroviral therapy, Sub-Saharan Africa

Background

Cryptococcal meningitis (CM) continues to cause significant morbidity and mortality in HIV infected individuals despite the scale-up of antiretroviral therapy (ART) in sub-Saharan Africa (SSA). Although it is well known that early initiation of ART during induction treatment of CM results in higher mortality (1, 2), data on outcomes for CM patients recently started on ART prior to presentation are few, and guidance on ART management in this group is based largely on expert opinion (3). Overall mortality appears to be similar comparing ART-experienced and ART-naïve cryptococcal meningitis patients (4-7). However, differences in presentation and outcomes for patients with 'unmasking' cryptococcal infection, where ART has been recently initiated, and those with virologic failure and/or non-adherence are not well described.

A recent large study in Uganda (8) found no difference in 2-week mortality between the ART-experienced and ART-naïve groups but there was increased short-term mortality in those receiving ART for less than 14 days compared with those on ART for more than 2 weeks, suggesting the possibility that pre-existing subclinical meningitis in some patients at ART initiation may drive an early unmasking immune reconstitution inflammatory response syndrome (IRIS) and increased mortality. The current study compared clinical presentation and short-term mortality outcomes for 678 ART-naïve and ART-experienced patients with a first episode of CM enrolled into the Advancing Cryptococcal meningitis Treatment for Africa (ACTA) trial in 4 countries in SSA (7). Mortality outcomes for patients receiving ART for varying durations prior to presentation were also compared.

Methods

Study setting and population

From January 2013 to November 2016, 721 HIV-infected adults (≥18 years old) from centres in Malawi, Zambia, Tanzania and Cameroon, presenting with a first episode of CM were prospectively enrolled into a randomized, noninferiority, multicentre trial (Advancing Cryptococcal Meningitis Treatment for Africa (ACTA), as previously described (7). The trial was approved by the London School of Hygiene and Tropical Medicine and country specific Research Ethics Committees. Written informed consent

was obtained from all participants or their closest relative (for those with abnormal mental status) prior to trial enrolment.

Study design

Patients were randomised to 1 of 3 treatment strategies: oral fluconazole plus flucytosine for 2 weeks, 1-week Amphotericin B (AmB)-based therapy, and standard 2 weeks AmB-based therapy (7). Those in the AmB arms were further randomized to flucytosine or fluconazole in a 1:1 ratio, as the partner drug given with AmB. Patients received consolidation fluconazole therapy after the 2-week induction period: 800mg until ART initiation or switch at 4 weeks and 400mg to 10 weeks. ART exposure was defined as ever having taken ART. Information on ART status and duration on ART was ascertained by self-report (or, where appropriate, from guardians) and confirmed by review of medical records.

Study outcomes and analysis

All-cause mortality at 2 and 10 weeks was compared based on ART status (experienced versus naïve) and ART duration at CM diagnosis. Baseline clinical and laboratory characteristics were compared across ART groups with Chi-square or Fisher exact tests for categorical variables and Kruskal Wallis tests for continuous variables. Unadjusted and adjusted cox proportional hazards models, Kaplan Meier curves and log rank tests were used to examine the hazard of mortality between ART-experienced and ART-naïve patients and for those on ART for varying durations. Adjusted models included known prognostic markers for poor outcome: age, baseline cerebrospinal fluid (CSF) fungal count (quantitative cultures (QCCs) calculated as described elsewhere (9)), Glasgow Coma Score (GCS) scale, CSF white blood cell count, haemoglobin, antifungal treatment (flucytosine versus non-flucytosine regimens) and recruitment site.

A distinct cut-off for the duration a patient has been taking ART to help distinguish between patients experiencing 'unmasking' CM and those with virologic failure/non-adherence has not been clearly defined. Results from Rhein et al (8) suggested an increased mortality for patients receiving ART for ≤14 days compared to those on therapy for 15-182 days or > 6 months. Therefore, we examined these time periods, and also conducted exploratory analyses to understand whether alternative time points with

a cut-off of 1 month, 2 months and 6 months could be used to distinguish sub-groups within the ART-experienced population, and identify any differences in mortality.
All analyses were performed in Stata version 15 ((StataCorp LP, College Station, TX)).

Results

Outcomes by ART status

A total of 678 patients were included in the study with 56% (381) ART-experienced at baseline (Fig 1). Overall, there was little difference in baseline demographics and clinical symptoms between ART-naïve and -experienced patients (Table 1), although both median viral load and median CSF fungal burden were higher for ART naive patients. All-cause mortality was similar at 2-weeks (17% vs 20%, p=0.39; HR 0.85, 95%CI 0.6-1.2, p=0.35), and 10 weeks (38% vs 36%, p=0.64; HR 1.03, 95%CI 0.8-1.32, p=0.82) for ART-experienced vs ART-naïve patients, respectively (Fig 1A), with similar results in adjusted analyses (data not shown).

Outcomes by ART duration

Overall, 66% of patients (251/678) had data on ART duration (Figure 1) with patients presenting with a first episode of CM at a median (IQR) time of 12 weeks (3 - 91 weeks) post ART initiation. In total, 19% (47/251) of patients had initiated ART within 2 weeks and 61% (152/251) within 6 months (Table 1, Table 2). There was similarity in the distribution of baseline demographics and clinical features between those taking ART for ≤2 weeks compared to those on ART for >2 weeks, though duration of headache was shorter for those taking ART for <2 weeks and CSF fungal burden was 1 log higher. Comparing survival curves there was a suggestion of increased short term mortality in those taking ART for <2 weeks, but there was no statistically significant difference in 2 week mortality (2-week mortality 23% vs 15%, p=0.15; HR 1.70, 95% CI 0.85 to 3.39, p=0.13), and 10-week mortality was very similar (34% vs 38%, p=0.59; HR 0.92, 95% CI 0.54 to 1.57, p=0.76) (Fig 2A, Fig 2B), with similar results in adjusted analyses.

Comparable results were obtained when ART duration was divided into ≤2 weeks, 15-182 days and >6 months, and, with a 1-month cut-off (Table 2). Higher viral loads and lower CD4 counts were identified for those reportedly on ART for >6 months compared to those on ART for shorter durations (Table 2), consistent with the possibility that the

former group had a higher proportion of non-adherent patients or patients who had developed ART resistance. There were no significant differences in 2- and 10-week mortality when exploring varying cut-off points for ART duration (Supplementary Table 1). Using a 1 month cut off, 2-week mortality was higher for those taking ART for ≤1 month (23% vs 14% 2-week mortality, p=0.08; HR: 1.74, 95%CI: 0.94 to 3.24, p=0.07) but this trend did not hold in the adjusted analysis (aHR: 1.44, 95%CI: 0.73 to 2.85, p=0.30).

Discussion

Over half the patients with a first episode of CM included in this study were ART experienced with 14% having started ART in the 2 weeks prior to diagnosis. There was no evidence for an overall difference in mortality between ART-naïve and -experienced populations at both 2 weeks and 10 weeks. Overall, ART-naïve patients had higher viral loads and fungal burdens. In exploratory analyses according to duration on ART, we did not identify a cut off for ART duration that led to significant differences in short term mortality, although there was a trend in the unadjusted analysis in this dataset for increased 2-week mortality for those taking ART for less than 1 month compared with those taking ART for >1 month, and the survival curves suggested the possibility of an increase in short-term mortality, between 1 and 2 weeks of antifungal treatment, in those taking ART for <2 weeks.

It should be noted that results from this study were limited by missing data for a number of patients for duration of taking ART and the fact that the definition for ART exposure was broad. This is because assessing ART compliance retrospectively is very difficult. While several measures of checking compliance are operational in most ART programs in SSA, drug compliance continues to be an important problem with levels of non-compliance ranging between 2% and 70% (10).

The size of our study is similar to that of Rhein and colleagues in Uganda (8) and the findings are in many respects similar in terms of the patient populations and differences, for example, in CD4 cell counts and cryptococcal CFU counts between groups. However, we did not find a significant difference in short-term mortality in those recently started on ART prior to presentation with cryptococcal meningitis, or as high a 2-week mortality

in those who had initiated ART within 2 weeks of presentation. This may simply be because both our studies were relatively small with 51 and 47 patients who had initiated ART within 2 weeks of presentation.

In addition, there were some differences in practice. In the study of Rhein, roughly a quarter of patients who had initiated ART within 2 weeks of presentation received corticosteroids and / or had ART withheld. In the ACTA trial, conducted prior to publication of the Uganda data, ART was not generally withheld in those starting ART within 6 months of presentation with meningitis and who reported and were assessed as adherent to ART. Corticosteroids were also not used in this group, in the light of the results of the CryptoDex study (11), which found them not to be beneficial, including in the subgroup of patients who had initiated ART within 3 months of meningitis diagnosis. Of note, if further data confirms an increased short-term mortality in those recently started on ART, we still do not know whether this would be abrogated by withholding ART or giving corticosteroids at the point of presentation.

Further work, ideally randomised studies, is clearly needed to inform guidelines on the most appropriate management for ART-experienced patients diagnosed with CM. Data from the ongoing AMBITION-cm trial (12), and indeed data from all 3 studies combined (7, 8, 12), may present a further opportunity to assess outcomes in patients on ART for various durations prior to meningitis. In the AMBITION-cm trial, based on a recent consensus among the investigators, including the team from Uganda, the current management strategy is to withhold ART for 4-6 weeks in those reportedly adherent and started or restarted on ART within the last 14 days, but to continue ART in those reportedly adherent and started or restarted on ART between 14 days and 6 months prior to presentation (3). Corticosteroids are not recommended. ART is also withheld in all non-adherent patients and all those on ART for > 6 months.

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Author contributions

NK RH JE CKa CKu ET SM SL DC SL TN AC MH OL SJ AL TH and SM conducted the study. TC and DW prepared the trial dataset. NK RH SM TH conceived this sub-study. NK and SM, with support from TC, analysed the data. NK SM RH TH drafted the manuscript. All authors critically reviewed and contributed to the final paper.

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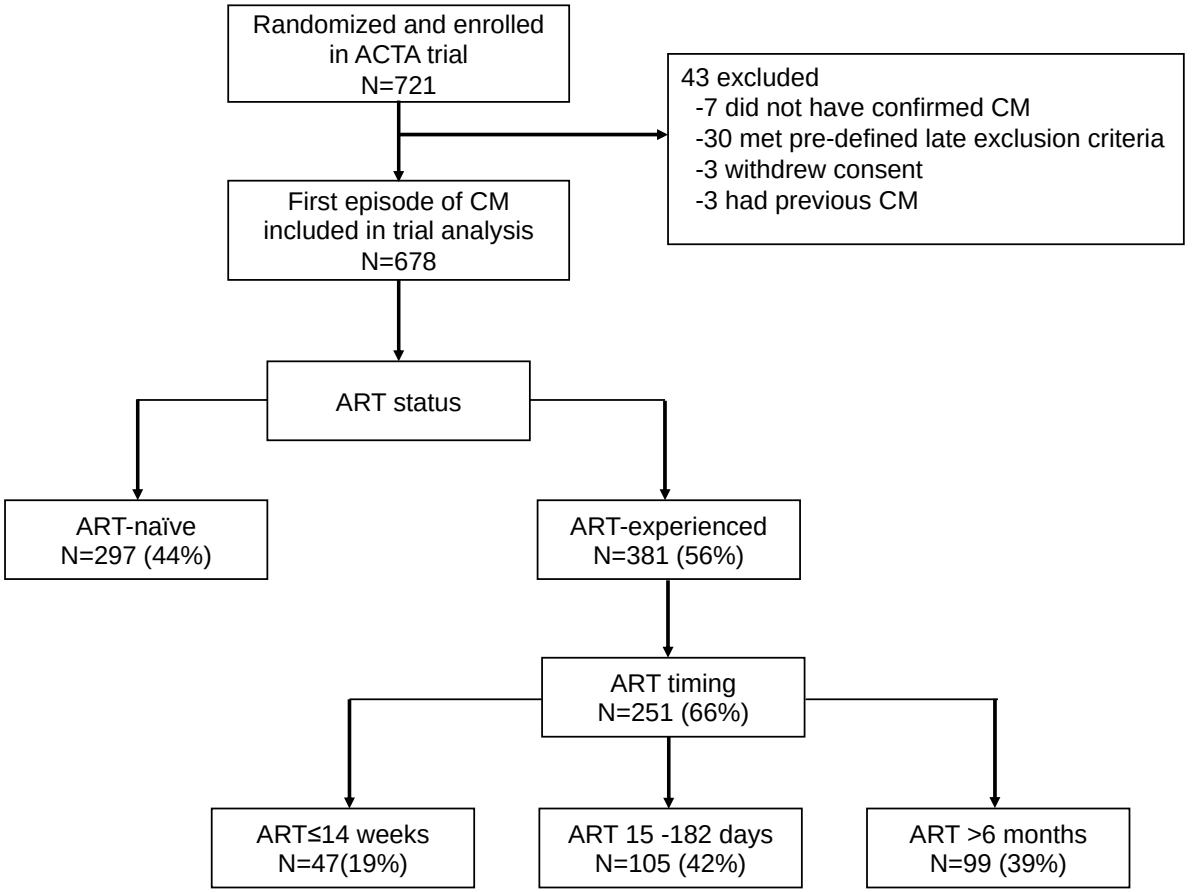

Figure 1: Study cohort

Table 1: *Clinical presentation and outcomes by ART status and ART duration.*

	ART status, no. (%) / median (IQR)			**ART duration, no. (%) / median (IQR)**		
	ART-naïve (N=297)	**ART-experienced** (N=381)	**p-value**	**≤2 weeks** (N=47)	**>2weeks** (N=204)	**p-value**
Demographics						
Male	173 (58%)	217 (57%)	0.74	30 (64%)	118 (58%)	0.45
Headache duration (days)	14 (7 to 21)	14 (7 to 28)	0.33	7 (7 to 20)	14 (7 to 30)	**0.03**
Seizures (within 72 hours)	54 (18%)	65 (17%)	0.70	9 (19%)	32 (16%)	0.56
Confusion	119 (40%)	148 (39%)	0.75	22 (47%)	74 (36%)	0.18
Current TB	36 (12%)	62 (16%)	0.13	8 (17%)	37 (18%)	0.86
Markers of HIV disease severity						
Anaemia (Hb<7g/dl)	5 (2%)	13 (4%)	0.16	2 (4%)	10 (5%)	0.84
CD4 count (cells/ml)	25 (10 to 55)	28 (10 to 68)	0.51	41 (22 to 83)	33 (12 to 78)	0.10
CD4 count <100 cells/ml	250 (91%)	312 (88%)	0.10	33 (81%)	164 (86%)	0.38
Viral load (log_{10} copies/ml)	5.4 (4.9 to 5.7)	4.0 (2.5 to 5.0)	**<0.001**	3.5 (2.9 to 3.9)	3.8 (2.2 to 4.9)	0.99
Markers of severe cryptococcal disease						
Age ≥50 (years)	34 (12%)	41 (11%)	0.77	7 (15%)	17 (8%)	0.17
GCS<15	76 (26%)	87 (23%)	0.41	15 (32%)	42 (21%)	0.10
CSF opening pressure >25mmCSF	125 (46%)	159 (45%)	0.73	21 (50%)	94 (49%)	0.88
CSF WCC <5 cells/ml	156 (56%)	199 (54%)	0.67	22 (51%)	108 (55%)	0.64

CSF fungal count (log_{10}CFU/ml)	5.2 (4.2 to 5.7)	4.7 (3.1 to 5.8)	**0.001**	5.2 (3.9 to 5.9)	4.2 (2.7 to 5.4)	**0.004**
Clinical management						
5FC-based antifungals	187 (63%)	226 (70%)	0.06	35 (75%)	137 (67%)	0.33
Number LPs received	3 (2 to 3)	3 (2 to 3)	0.9	3 (2 to 5)	3 (3 to 4)	0.68
CSF clearance rate	0.34 (0.23 to 0.50)	0.33 (0.22 to 0.50)	0.82	0.36 (0.27 to 0.63)	0.32 (0.22 to 0.47)	0.06
All-cause mortality						
2 weeks	59 (20%)	66 (17%)	0.39	11 (23%)	30 (15%)	0.15
10 weeks	107 (36%)	144 (38%)	0.64	16 (34%)	78 (38%)	0.59

Abbreviations: LP: Lumbar puncture 5FC: Flucytosine WCC: White cell count Hb: Haemoglobin CFU: Colony forming units CSF: Cerebrospinal fluid

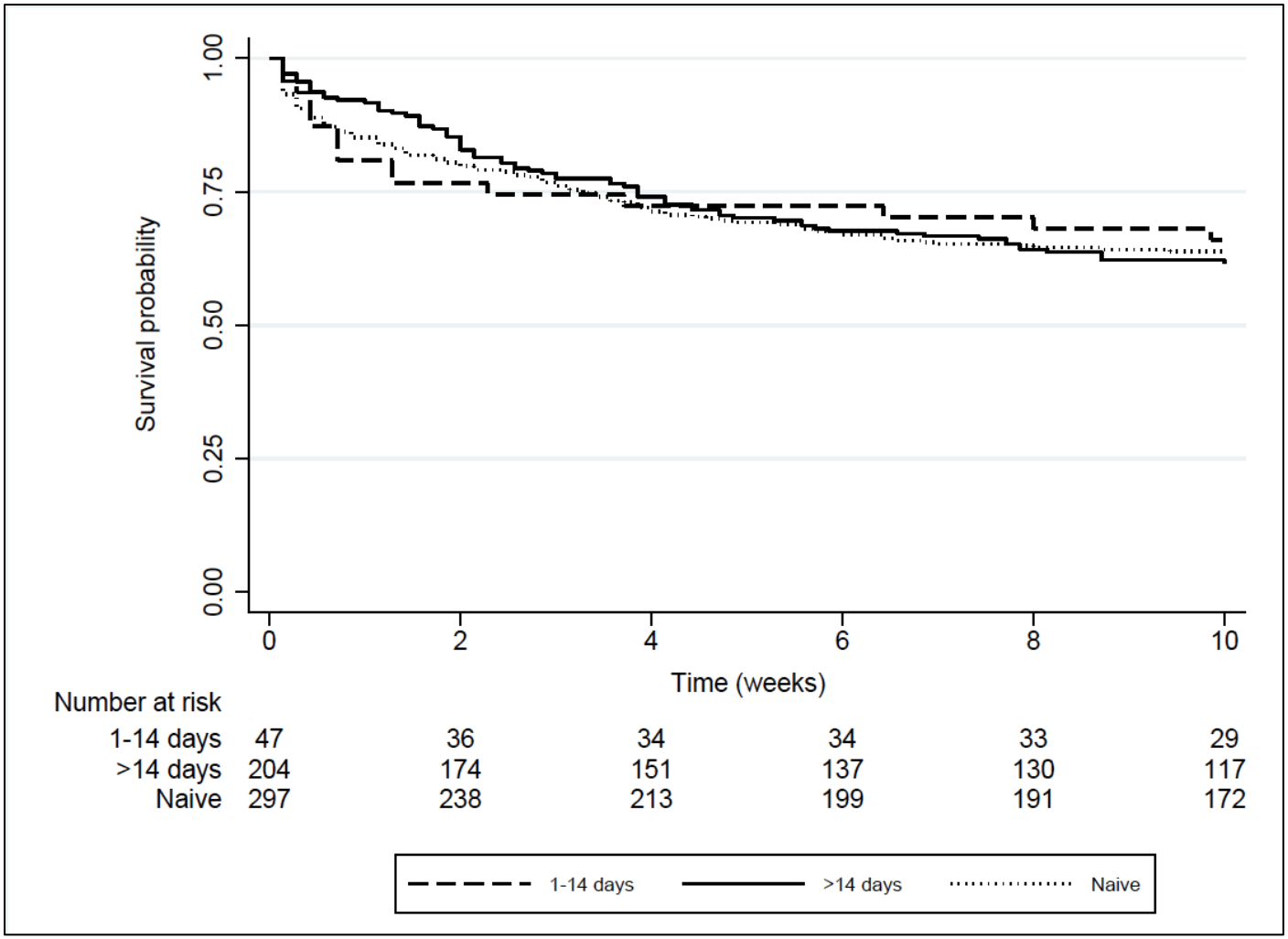

Fig 2: A. *Kaplan Meier surivival plot by ART status.*

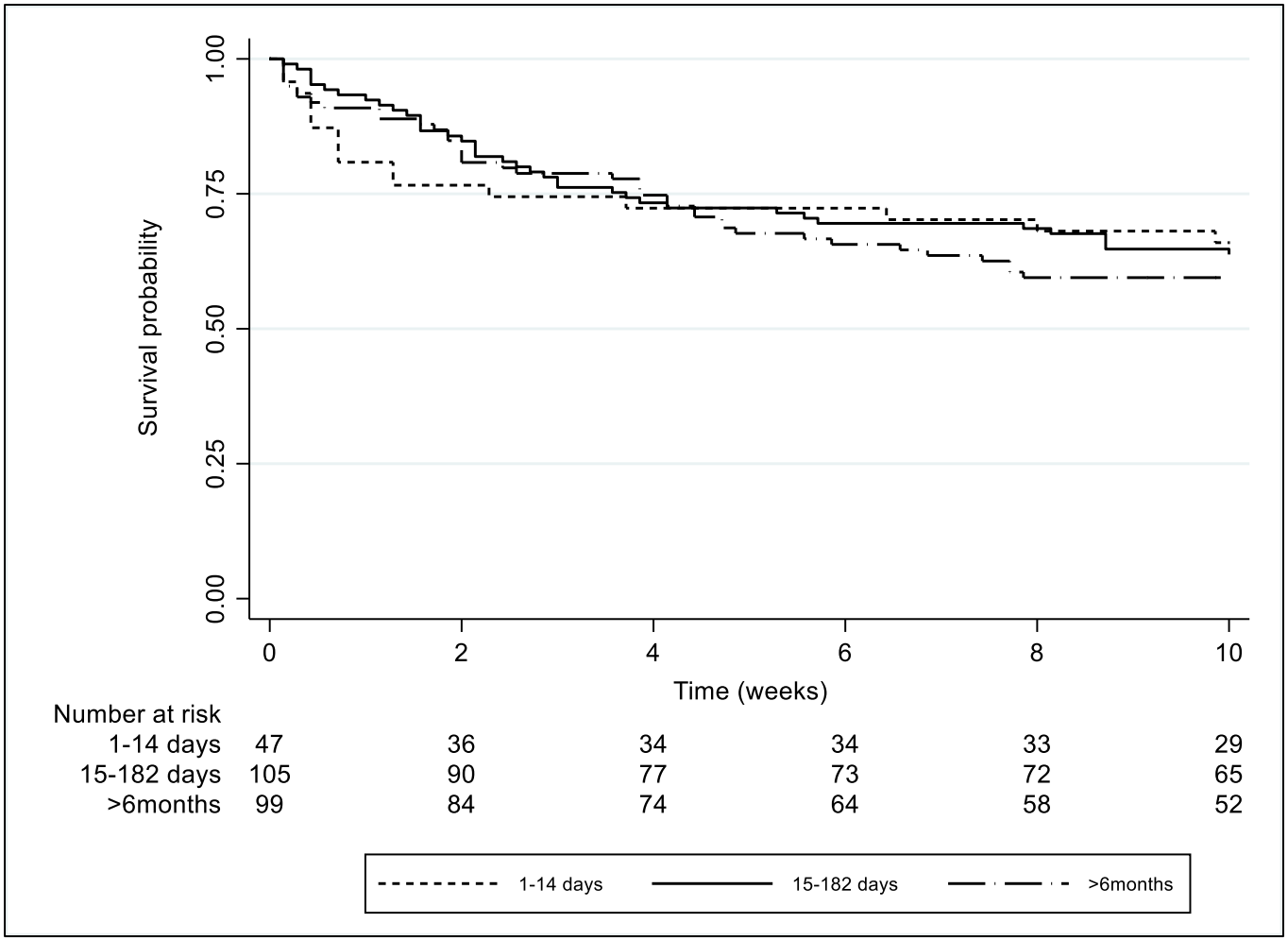

Fig 2: B. *Kaplan Meier survival plot by ART timing*

Table 2: Clinical presentation and outcomes by ART duration at varying cut-off points

	ART duration						
	≤14 days (N=47)	**15-182 days** (N=105)	**>6 months** (N=99)	**p-value**	**≤1 month** (N=75)	**>1 month** (N=176)	**p-value**
Demographics							
Male	30 (64%)	60 (57%)	58 (59%)	0.74	47 (62%)	101 (57%)	0.44
Headache duration (days)	7 (7 to 20)	14 (7 to 30)	14 (7 to 21)	0.04	10 (7 to 21)	14 (7 to 30)	0.07
Seizures (within 72 hours)	9 (19%)	18 (17%)	14 (14%)	0.72	32 (43%)	64 (36%)	0.35
Confusion	22 (47%)	43 (41%)	31 (31%)	0.15	13 (17%)	28 (16%)	0.78
Current TB	8 (17%)	22 (21%)	15 (15%)	0.55	11 (15%)	34 (19%)	0.38
Markers of HIV disease severity and control							
Hb<7g/dl	2 (4%)	9 (9%)	1 (1%)	**0.04**	5 (7%)	7 (4%)	0.37
CD4 count (cells/ml)	41 (22 to 83)	53 (20 to 85)	21 (7 to 52)	**<0.001**	48(22 to 93)	32(11 to 68)	**0.01**
CD4 count <100 cells/ml	33 (81%)	78 (82%)	86 (90%)	0.24	52 (79%)	145(87%)	0.10
Viral load (log_{10} copies/ml)	3.5 (2.9 to 3.9)	2.6 (2.1 to 4.6)	4.7 (2.8 to 5.3)	**0.01**	3.2 (2.8 to 3.9)	4.4 (2.1 to 5.0)	0.35
Markers of severe cryptococcal meningitis							
Age ≥50 (years)	7 (15%)	11 (11%)	6 (6%)	0.22	12 (16%)	12 (7%)	**0.02**
GCS<15	15 (32%)	22 (21%)	20 (20%)	0.25	21 (28%)	36 (23%)	0.19

CSF opening pressure >25mmCSF	21 (50%)	44 (44%)	50 (53%)	0.47	31 (45%)	84 (51%)	0.43
CSF WCC <5cells/ml	22 (51%)	55 (54%)	53 (56%)	0.84	37 (52%)	93 (55%)	0.65
CSF fungal culture (log_{10} CFU/ml)	5.2 (3.9 to 5.9)	3.6 (1.8 to 5.0)	4.9 (3.6 to 5.7)	**<0.001**	4.8 (3 to 6)	4.2 (3 to 5)	0.11
Clinical management							
5FC-based antifungals	35 (75%)	71 (68%)	66 (67%)	0.62	54 (72%)	118 (67%)	0.44
Number LPs received	3 (2 to 5)	3 (3 to 4)	3 (3 to 5)	0.26	3 (3 to 4)	3 (3 to 4)	0.21
CSF clearance rate	0.36 (0.26 to 0.63)	0.32 (0.22 to 0.41)	0.31 (0.22 to 0.47)	0.15	0.34 (0.24 to 0.62)	0.32 (0.22 to 0.47)	0.12
Mortality							
2 weeks	11 (23%)	15 (14%)	15 (15%)	0.34	17 (23%)	24 (14%)	0.08
10 weeks	16 (34%)	38 (36%)	40 (40%)	0.71	30 (40%)	64 (36%)	0.59

Abbreviations: WCC: White cell count Hb: Haemoglobin CFU: Colony forming units CSF: Cerebrospinal fluid

Supplementary Table 1: ART duration cut-off point exploratory analysis

ART duration	2-week mortality	p-value	10-week mortality	p-value
≤7days >7 days	4 (17%) 37 (16%)	0.89	6 (26%) 88 (38%)	0.24
≤14 days >14 days	11 (23%) 30 (15%)	0.15	16 (17%) 78 (82%)	0.59

≤1month >1 month	17 (23%) 24 (14%)	0.08	30 (32%) 64 (68%)	0.59
≤2month >2 months	21 (21%) 20 (13%)	0.12	40 (43%) 54 (58%)	0.56
≤6month >6 months	26 (17%) 15 (15%)	0.68	54 (58%) 40 (42%)	0.44

Abbreviations: IQR: Interquartile range